area and low recoil after PTCA reduced the restenosis rate. In order to reduce the recurrence rate, lesions with high recoil and a low LA should receive stents with optimum expansion.

995 Basic Studies in Cardiomyopathy

Tuesday, March 18, 1997, Noon–2:00 p.m.
Anaheim Convention Center, Hall E
Presentation Hour: Noon–1:00 p.m.

995-58 Apoptosis in Cardiomyopathy

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Fas/Fas ligand interactions serve as a signaling pathway for apoptosis. We elucidated the role of apoptosis on the progression in myocardial damage in dilated (DCM) and hypertrophic cardiomyopathy (HCM). *Methods:* Total 34 patients (DCM:15, HCM:16 and normal control (N):3) were entered and cardiac cathetelization and endmyocardial biopsy (EMB) were performed. All samples were serially sectioned and analyzed pathologically. Expression of Fas antigen was investigated using immunostaining with polyclonal anti-Fas antibody and the intensity of Fas expression was graded semiquantitatively (0 point: none ~ 3: > 30%). For the detection of apoptic cells, *in situ* TdT staining was performed. Each 6 pieces of magnified photographs were used for counting the number of apoptic cells. For clinical application, the relation between hemodynamic parameters of cardiac function and immunohistological results were investigated statistically. *Results:* The intensity of Fas antigen on myocardium in DCM (218 ± 0.19) was significantly higher than that of HCM (1.33 ± 0.23, $p < 0.05$), while the intensity of Fas antigen in N (0.33 ± 0.33) was significantly less than both groups. The mean incidence rate of apoptic cells in DCM was also higher (15.56 ± 3.24%) than that of HCM (10.40 ± 1.74%), and the apoptic cells corresponded with Fas positive cells. No apoptic cell was found in N. The incidence rate of apoptic cells was higher in the patients with lower EF (≤ 30%, 9.29 ± 1.62%) than the patients with higher EF (> 30%, 24.17 ± 5.12%, $p < 0.05$). *Conclusion:* These results suggest that apoptosis might play a role on the progression in myocardial damage especially in DCM, and Fas system may mediate an apoptosis in cardiomyopathy.

995-59 Role of Nitric Oxide in Acute Adriamycin Toxicity

I. Tritto [1], D. D'Andrea, A. Scognamiglio, C. Battaglia, P.P. Elia, C. De Simone, A. Violante, M. Chiariello, G. Ambrosio [1]. *Division of Cardiology, University of Naples, Italy,* [1] *Division of Cardiology, University of Perugia, Italy*

Adriamycin (ADR) cardiotoxicity has been related to oxygen radical (OR) generation. However, the exact mechanism of this phenomenon is still unknown. We have recently shown that exposure to ADR severely impairs both endothelium dependent and independent vasodilation in isolated vessels, and that this toxic effect was prevented either by OR scavenging, or by inhibiting nitric oxide formation. These findings indicate that both ORs and nitric oxide play a role in mediating ADR vascular toxicity, most likely through formation of the powerful oxidant peroxynitrite. In the heart, we have previously demonstrated that acute ADR toxicity can be prevented by OR scavenging. To test whether nitric oxide is also involved in acute cardiac ADR toxicity, isolated rabbit hearts were perfused with 300 μM ADR for 60 min, followed by 20 min wash-out (ADR; n = 6). Another group received ADR plus the nitric oxide synthase inhibitor N^{ω}-nitro-L-arginine methyl ester (L-NAME, 300 μM; n = 7). ADR infusion markedly affected left ventricular function. In fact, at the end of wash-out left ventricular developed pressure (DP) was 32 ± 15%, and end-diastolic pressure (EDP) was 643 ± 239% of baseline. Administration of L-NAME largely prevented both alterations; these effects persisted after L-NAME wash out (DP 79 ± 7%, EDP 206 ± 38% of baseline; $p < 0.05$ vs ADR). In additional experiments we verified that L-NAME has no oxygen radical scavenging property. These data show that the acute impairment of contractile function induced by ADR in isolated hearts can be prevented by inhibiting nitric oxide synthesis. Taken together with previous data showing that cardiac ADR toxicity can also be prevented by OR scavengers, these results support the hypothesis that also in the heart acute ADR toxicity could be mediated by peroxynitrite, formed in the reaction between oxygen radicals (generated by ADR) and nitric oxide.

995-60 Proinflammatory Cytokine mRNA and Protein Expression in Acute Chagasic Cardiomyopathy

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Acute Chagasic cardiomyopathy follows infection by the flagellate *Trypanosoma cruzi,* and is felt to represent an inflammatory condition disproportionate to the cardiac burden of organisms. The degree of production of proinflammatory cytokines within the infected myocardium, and the time course of their expression, is not known. Accordingly, we studied one month-old male Lewis rats inoculated with cell culture-derived *T. cruzi* trypomastigotes. Rats were killed 36 hours (h), 5, 10 and 15 days after infection (n = 6/group). Saline injected rats were used as control (n = 6). Hearts were collected for histology, mRNA, and protein analyses. Histologic analysis of myocardium showed few changes 36 h post inoculation (p.i.); by day 5, dense intracellular infection with amastigotes and a minimal inflammatory infiltrate was noted. On day 15, dense infection and diffuse inflammatory infiltrate was seen. Northern blots of total RNA (densitometry; ratio of specific gene to 28S rRNA; mean ± SEM) showed no signal for IL-1β or TNF-α, and a weak signal for IL-6 (0.32 ± 0.1) in control hearts, and high levels of expression for the three genes at 36 h p.i. (IL-1β, 0.47 ± 0.2; IL-6, 0.69 ± 0.2; TNF-α, 0.67 ± 0.24). By day 5, TNF-α mRNA levels were the highest, while IL-1β and IL-6 (1.8-fold) levels increased substantially and peaked by the 10th day (by at least 2.6-fold). On day 15, IL-1β and IL-6 levels still remained high but of TNF-α fell. Western blots showed similar results as that of mRNA, except that TNF-α levels remained high even at 15 day p.i. *We conclude:* In addition to mechanical damage by *T. cruzi,* substantial proinflammatory cytokine production within the myocardium participates in the pathophysiology of acute Chagasic cardiomyopathy. These proteins may contribute to myocardial contractile dysfunction in this condition.

995-61 Arginine Vasopressin-V1a Receptor mRNA Levels are Reduced in the Failing Rat Myocardium

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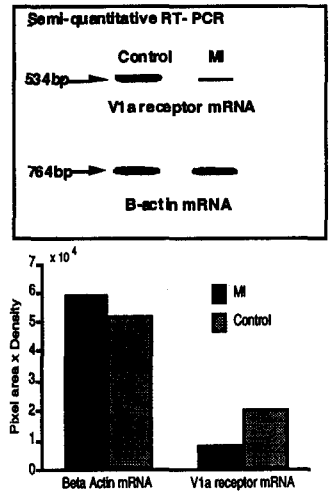
Arginine Vasopressin (AVP) is increased in congestive heart failure (CHF) but it is unknown if this causes down-regulation of the cardiac AVP-V1a receptor. We have previously found that the functional effects (in terms of mechanical function and intracellular calcium transient kinetics) of a specific V1a agonist were reduced in isolated cardiomyocytes from rats with CHF, suggesting "functional down-regulation" of the V1a receptor, but the mechanisms were unclear. We therefore isolated and quantitated V1a receptor mRNA (using RT-PCR with V1a receptor specific primers) from the myocardium of 2 groups of rats (n = 4) – CHF, 8 weeks after an anterior infarct (LV developed pressure 120 ± 5.0 vs 101 ± 3 mmHg & LVEDP 6 ± 2 vs 14 ± 2 mmHg; Sham vs CHF, respectively) & matched sham operated rats. V1a receptor mRNA levels were significantly reduced in the heart failure rats compared to sham rats while beta actin mRNA levels were no different.



These data suggest for the first time that AVP-V1a receptor mRNA is reduced in the failing adult rat myocardium & the "functional down-regulation" of the AVP-V1a receptor seen in cardiomyocytes may have a pre translational mechanism.

TUESDAY POSTER